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During this grant period, a linear-quadratic random effects model of the profile of PSA levels in men following radiation therapy for prostate cancer was developed. It can be used to predict, for a new patient, the expected trajectory of future PSA levels, and the probability of biochemical failure. The model, which includes terms for initial PSA, post-treatment PSA nadir, time of nadir, and future PSA level, also allows us to update these predictions as new PSA measurements on the patient are collected. We show that our method has some advantages over the widely used definition of biochemical failure as three consecutive rises in post-nadir PSA level.

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Introduction

The public abstract in the original grant proposal reads as follows:

The definition of disease relapse following definitive radiation therapy for localized prostate cancer is a critical issue in the initial selection of salvage therapy as well as in the identification of patients in whom adjuvant therapy may be necessary. In September 1996, a panel of clinicians agreed on a definition of biochemical failure based on three consecutive rises in serial post-therapy serum prostatic antigen levels (Cox et al, 1997). The validity of the consensus definition has been questioned since its inception, leading to confusion and anxiety for patients as well as their physicians (Taylor et al, 2001).

The principal investigator of the proposed research developed a model to classify prostate cancer patients according to disease relapse following definitive radiation therapy (Hanlon, 1998). The model was developed and tested statistically using a subset of 35 patients with relatively homogenous tumor and treatment characteristics: men presenting with pretreatment PSA levels between 10 and 19.9 ng/mL and treated with three dimensional conformal radiation therapy. In order to evaluate the clinical utility of the model, we propose to apply it to a much larger population of men that represent all stages of presenting disease. The specific aim of the proposed research is to validate our classification model by applying it to an existent database of 261 prostate cancer patients via the modeling of covariates, including tumor differentiation as defined by Gleason Score, palpation tumor stage, and pre-treatment PSA. We propose an analysis of predictors of post-nadir rise, as salvage therapy strategies are often designed around the rate of increase in PSA levels post-nadir. Similarly, we propose an analysis of predictors of initial decline and its relationship to outcome, as this may be useful in defining early intervention strategies for relapse. The validity of the modeling will be assessed by comparing biochemical classification to clinical results as obtained from biopsy. An analysis will be performed to assess the time it takes to acceptably stratify patients according to post-treatment disease status.

The proposed research will provide insight into the much-debated issue of prostate cancer "relapse". Such insight could have tremendous implications in defining treatment strategies for salvage therapy. It has advantages over the much-disputed clinical classification, including the lack of clinical bias, noise insensitivity, and the ability to predict treatment failure at earlier points in time. The proposed research also has relevance in the area of quality of life, as the debate over relapse is the source of significant anxiety for both patients and treating physicians.

Body

Within the department of Radiation Oncology at Fox Chase Cancer Center, 533 men were treated between 4/89 and 12/99 for prostate cancer and were the basis of a training set for a linear-quadratic random effects model. The patients had a mean of 11.9 PSA observations each. A quadratic-linear spline model with non-linear random effects was fitted to the 533 observed PSA profiles (Davidian and Giltinan, 1995). To evaluate the predictive ability of the model, the following procedure was used: for each subject in turn, a prediction of time of biochemical failure was made using each of two definitions.

One definition, which is widely used in clinical practice, is three consecutive rises in post-nadir PSA levels. The other definition, which is derived from the spline model, is a rise of a specified amount of the post-nadir predicted PSA level.

Our current research includes a Bayesian approach to classifying the prostate cancer patients according to disease relapse using a class of hierarchical nonlinear mixed effects models. The goal is to generalize the work of Hanlon (1998) by accounting for patient's specific characteristics in the model. For $i = 1,\ldots,m$, $j = 1,\ldots,n_i$, let y_{ij} be the jth post treatment PSA level for patient i and a_i be the vector of observed covariate values corresponding to individual attributes for patient i. Based on the model analyzed by Hanlon (1998), we assume that

$$
\begin{aligned}
&y_{ij} = g(\alpha' z_i) + \beta_1 \exp(-\beta_2 t_{ij}) + \beta_3 \exp(b_i t_{ij}) + e_{ij}, \\
&b_i \sim pN(\mu_1, \sigma_b^2) + (1-p)N(\mu_2, \sigma_b^2), \\
&e_i \sim N(0, \sigma^2 I_{n_i}), \\
&b_1,\ldots,b_m, e_1,\ldots,e_m \text{ independent},
\end{aligned}
$$

where α is a k-dimensional vector of covariate effects, g is a known link function, and $e_i = (e_{i1}, e_{i2},\ldots,e_{in_i})$. The Bayesian approach consists of putting a "hyperprior" distribution on $\theta = (\sigma^2, p, \alpha, \mu_1, \mu_2, \beta_1, \beta_2, \beta_3, \sigma_b^2)$ then estimate the joint posterior density of $(\theta, b_1,\ldots,b_m)$ given the data $\{(y_i, a_i), i = 1,\ldots,m\}$. The marginal posterior density of p is of particular interest for classification purpose. Upon specification of the prior density, the posterior distribution will certainly be intractable due to the nonlinearity of the mean response as a function of time. We are working to develop a Metropolis-Hastings based algorithm to estimate features of the posterior distribution and investigating the feasibility of implementing this Bayesian model in Bugs.

A classical choice of priors for σ^2 and σ_b^2 are inverse gamma distributions and we take independent normal priors for μ_1 and μ_2 with large variances. A multivariate normal prior with small precision will be put on the vector of covariate effects α and independent gamma distributions on $(\beta_1, \beta_2, \beta_3)$. We also assume that $p \sim U(0,1)$ reflecting no *a priori* knowledge on the clinical classification of the patient. In order to select the function g, we first plan to fit the above model (within the Bayesian framework) in the absence of covariate information. After we obtain the Bayes estimates for $(\beta_1, \beta_2, \beta_3, b_1,\ldots,b_m)$, we plot the predicted values $\widehat{y_{ij}}$ versus each covariate to help us choose the function g. This of course is an *ad hoc* procedure but it should narrow the search for reasonable link functions to a much smaller class. Bayesian model selection techniques will be used to select the model with the "best" link function g.

Key Research Accomplishments

- A linear-quadratic random effects model of the profile of PSA levels in men following radiation therapy for prostate cancer was developed. The model can be used to predict, for a new patient, the expected trajectory of future PSA levels, and the probability of biochemical failure. The model, which includes terms for initial PSA, post-treatment PSA nadir, time of nadir, and future PSA level, also allows for updated predictions as new PSA measurements at the patient level are collected.

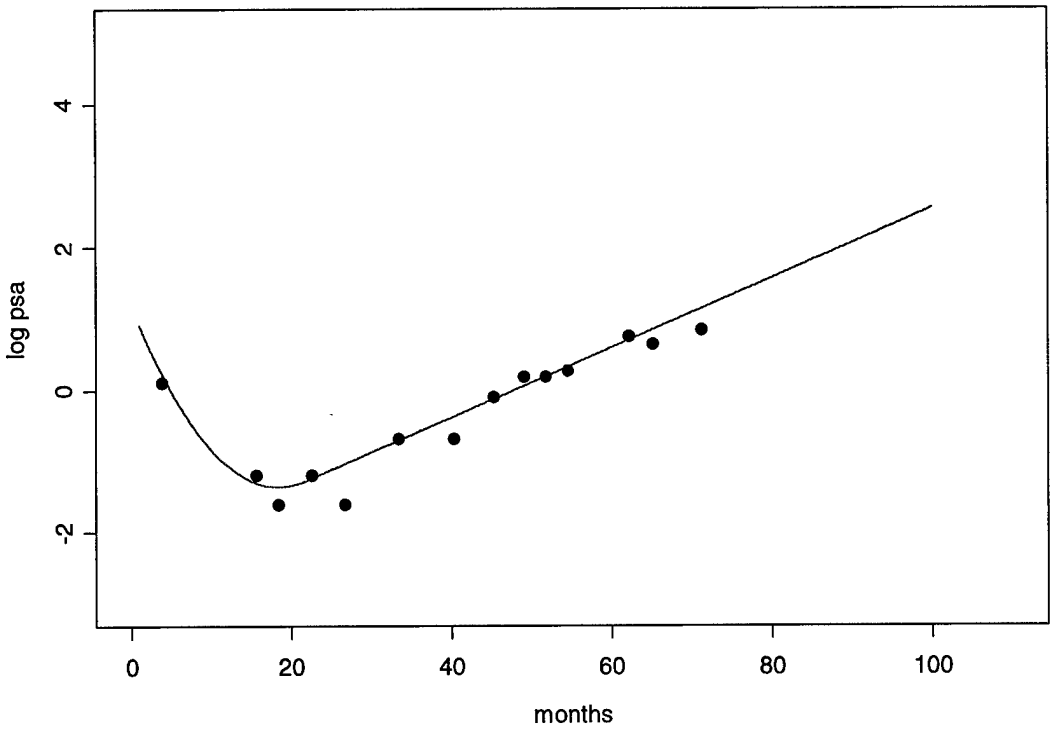
Reportable Outcomes

Thirty-three percent (78/533) of the subjects experienced biochemical failure as defined by three successive rises in post-nadir PSA, and 31% (167/533) of the subjects experienced a rise of 1.8 units of log PSA levels in 5 years following PSA nadir. The critical value of 1.8 units was chosen to make the model-based predicted failure rate comparable to that produced by the "three successive rises" method. The two prediction methods produced the same prediction in 444/533 subjects (83%) and produced opposing predictions in the remaining 17% of subjects. In the 128 cases when both methods predicted biochemical failure, the model-based method predicted it earlier in 66 subjects, while the "three rises" method predicted it earlier in just 20 subjects. Both methods predicted failure at the same time in 42 subjects.

Conclusions

Our database of the PSA profiles of 533 patients may be used as a training set to develop a predictive model for the future PSA trajectory for a new patient, and the prediction may be updated as new PSA information is acquired. A critical value may be defined in terms of a predicted rise of 1.8 units of log PSA level over 5 years, yielding a predicted biochemical failure rate of 31%. The "three successive rises" method has two important disadvantages when compared to the spline model prediction method: a slow but steady increase in post-nadir PSA levels will be classified as a failure under the "three rises" method, but may not signify a clinically meaningful rise within a patient's expected lifetime; and a patient with highly variable post-nadir PSA levels may experience a clinically significant rate of increase in PSA levels, but never experience three significant rises. For example, Figure 1 presents a patient with clear biochemical failure, as shown by the predicted profile (solid line), but there are never three consecutive rises in the PSA levels. Model-based prediction methods such as the one presented here hold promise as enhanced tools for predicting biochemical failure.

Fig. 1. Patient with biochemical failure without three successive rises



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Appendices

None